REMARKS

Attached hereto is an Appendix showing the changes made to claims 5 and 9, as amended.

Claims 5 and 9 have been amended to expedite prosecution by defining the fragment as specified in claim 3 and deleting the word "unique." New claims 39 and 40 have been added to more particularly claim the cDNA molecule of the present invention. This is supported throughout the specification, for example at pages 6-8, page 36, lines 29-30 and pages 51-54. Consequently, these amendments do not introduce new matter and their entry is respectfully requested.

Claims 5-11 were rejected under 35 U.S.C. §112, first paragraph.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Claims 5-11 were rejected on the basis that the specification does not enable "unique fragments" of hMSH5 (claims 5-9) or synthesis of hMSH5 (claims 10-11). Applicants respectfully submit that the specification clearly teaches how to determine what a unique fragment is. Namely, by using a public database to identify fragments that had not been identified as of the filing date in a public database (see pages 35-36). However, to expedite prosecution applicants are using an alternative fragment definition. Thus, as amended, the rejection has been obviated.

Applicants respectfully submit that the specification provides ample guidance to the skilled practitioner to synthesize a human mismatch repair gene, particularly hMSH5. The specification provides **extensive** teaching regarding the sequence of hMSH5, including the structure and sequence of the introns as well as the coding sequence of the gene itself. More particularly, the specification teaches the hMSH cDNA (SEQ ID NO:1) at pages 51-54, the 5' intron/exon borders (SEQ ID NOs:3-26) at pages 55-56, the 3' intron/exon borders (SEQ ID NOs: 27-50) at pages 56-57, the size of each of the 25 hMSH5 exons at page 57, and the sequence of each of the 24 hMSH5 introns (SEQ ID NOs: 55-85) at pages 61-67. In addition, the specification teaches primers (SEQ ID NOs: 51 and 52) to isolate the hMSH5 gene from a genomic library. In addition to providing this extensive sequence information, the specification teaches how to use PCR to identify allelic variations. For example, using SEQ ID NOs: 3-50 to amplify specific exons or introns at page 10. The specification further teaches how to design additional primers to amplify individual introns or exons of hMSH5 at page 43, including how to specifically identify alterations in a MSH5 gene at pages 43-44. Thus, applicants respectfully submit that the specification enables the skilled practitioner to synthesize a human mismatch repair gene, particularly hMSH5. Moreover, as

claimed there is no indefiniteness problem. Claims 10 and 11 are specifically directed to kits that can be used to amplify sequences within MSH5.

Accordingly, in view of the foregoing, applicants respectfully submit that all claims comply with 35 U.S.C. §112, first paragraph.

Claims 2-6, 8 and 9 were rejected under 35 U.S.C. §102(b) as being anticipated by Sargent et al. (EMBO J. 8:2305-12 (1989)).

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The Examiner has indicated that one of the "genes" Sargent identified on one of two cosmids, the "G7 gene," is inherently the hMSH5 gene and "[t]herefore, it clearly appears that the Sargent cosmid vectors anticipate the current claims as inherently comprising the MSH5 gene sequence." However, as explained below, there is no homology with what Sargent taught on the G7 gene and the homology between the so-called "G7 gene" and hMSH5 is only apparent by using a sequence of the "G7 gene" disclosed in 1999. Thus, there was nothing disclosed in Sargent that would suggest, let alone teach, the presence of the hMSH5 gene on one of the cosmids.

Rather, Sargent discloses two overlapping cosmids from the MHC class III region, which together represent **541 kilobases (kb)** of human genomic DNA. These cosmids were isolated by the technique known as chromosome walking, using the technique within the human MHC class III region by using probes to several known genes (including *Factor B*and *CYP21*) and 13 walking probes. Chromosome walking involves isolating overlapping clones of DNA segments based on homology at the sites of overlap, allowing the practitioner to assemble a rough map of a region of DNA, such as shown in Figure 1 of Sargent. However, the map generated by chromosome walking is a vague map setting forth some identifying locations and little specific detail. By itself, the existence of a map of a series of overlapping clones imparts no information regarding the existence of any genes within that area, let alone their structure or function. Sargent provides absolutely no sequence data for any of the 541 kb genomic region.

The "G7 gene" disclosed in Sargent in fact teaches away from the present invention, because this "gene" was subsequently found by Sargent's group to be a different gene. The last named author of Sargent was a co-author of Albertella et al., also relied upon by the Examiner. As explained below, Albertella followed up on the work identified by Sargent with further mapping of the G7 gene.

There appears to be some confusion in the rejection because the area around the G7 gene has subsequently been shown to contain at least three other genes. To identify coding regions within these cosmids, Sargent hybridized DNA probes to a preparation of total RNA to identify potential transcripts of mRNA (Figure 5). However, because Sargent did not select mRNA from the preparation of **total** RNA before the hybridization, the resulting bands did not necessarily represent mRNA transcripts of a single gene. Indeed, that is apparent with the G7 area. Sargent reported 13 genes based on bands on Northern blots of total mRNA (Table 1), two of which represented known genes and 11 of which were novel. Partial or full-length cDNA clones were reported for 8 of the 11 novel genes; the "G7 gene" was not one of them. Thus, Sargent did not report a pure mRNA or cDNA; there was no purified "G7 gene" represented, and it was not known where to sequence. In fact, the complexity of this genomic area is underlined by the fact that it took another 10 years for that group to publish the sequence of the G7 area (submitted to Genbank on August 6, 1999 as accession number AJ245661).

Albertella, as discussed above, followed up on the work reported in Sargent by further mapping the G7 area (amongst others). Indeed, one purpose of Albertella was to find if there were more genes in the area because by this time it had become clear that other areas of the MHC class III region contain very densely packed clusters of genes. "The detection of this additional gene within a known gene-dense region suggested the possibility that other areas of the current map ...should be reexamined for the presence of genes." By the time of Albertella, the G7 region was known to contain at least two genes, as shown by their use of the term G7 and G7a. Using exon trapping and PCR, Albertella reported an additional two genes were found within the "G7 gene": G7c and G7d.

Thus, as shown in Figure 4 of Albertella, the "G7 gene" in fact contains 4 genes: designated G7a, G7c, G7d, and G7. While the Examiner contends that it is the G7 gene itself which is homologous to hMSH5, as shown in the blast comparison in the office action, no sequence for a gene homologous to MSH5 was shown. Rather, Albertella teaches the primers used to amplify G7c and G7d which would suggest to the skilled artisan that the so-called G7 gene in Sargent was likely one of the two specific genes now identified. In fact, the G7 sequence information which the Examiner used to claim homology to hMSH5 was not submitted to Genbank until August 6, 1999 well after the hMSH5 sequence was provided. Thus, neither Sargent nor Albertella teaches hMSH5, or any sequence information which could be used to obtain any part of hMSH5.

The Examiner's argument that a 2.9 kb gene that lies within a 541 kb region and thus "inherently comprises" the claimed hMSH5 gene is not what is claimed. For example, claim 2 is directed to "An isolated and purified nucleotide segment." The hMSH5 gene represents roughly 0.5% of this genomic region, and thus is not isolated or purified from other sequences within that region. Claim 3 is directed to an isolated fragment of SEQ ID NO:1. Sargent simply does not teach such a fragment. Similarly, claim 4 is directed to an isolated DNA segment of SEQ ID NOs:3-52, the **longest** of which is 29 base pairs (or .029 kb, representing 0.005% of the region) and thus, Sargent is not "isolated." Claim 5 specifies that the isolated DNA segment hybridizes to SEQ ID NO:1 under stringent conditions. The genome cosmid of Sargent does not meet such criteria. There is no such vector described in Sargent. Sargent in no way discloses a host transformed by such a vector or an antisense vector. Applicants have added new claims 39 and 40, directed to an isolated and purified nucleotide segment of SEQ ID NO:1, which represents the sequence of the cDNA (or mRNA); such a nucleic acid is clearly not anticipated by the Sargent cosmid vectors which are genomic.

Accordingly, in view of the foregoing, applicants respectfully submit that all claims comply with 35 U.S.C. §102(b).

Claims 10-12 were rejected under 35 U.S.C. §103(a) as being obvious over Albertella et al. (Genomics 36:240-51(1996)) in view of the Stratagene Catalog (1988), p. 39.

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

The Examiner has rejected claims 10-12 on the basis that Albertella discloses primers that amplify the "G7 gene region." However, as discussed above, Albertella teaches that the primers amplify G7c and G7d, neither of which is homologous to hMSH5. Thus, it could not have been obvious that the primers disclosed in Albertella could be used to amplify hMSH5, because they do not amplify hMSH5 but instead amplify the G7c and G7d genes. Similarly, there would be no motivation to provide such primers in a kit to amplify hMSH5.

Claim 7 was rejected under 35 U.S.C. §103(a) as being unpatentable over Sargent et al. (EMBO J. 8:2305-12 (1989)) in view of Beach et al. (U.S. Patent No. 6,025,192).

Applicants respectfully submit that this rejection should be withdrawn for the following reasons.

Again, the Examiner has taken the position that hMSH5 is the "G7 gene" disclosed in Sargent and thus the Sargent cosmids inherently contain hMSH5. However, as described above, the G7 region was not characterized in Sargent, and in fact Sargent teaches away from the present invention because it characterized a single "G7 gene" which in fact contains at least 4 genes, not 1. Furthermore, the vector of claim 7 contains the **isolated** DNA segment of claim 5. As previously stated, the 2.9 kb or smaller DNA of claim 7 is hardly isolated in the Sargent cosmid. Thus, Sargent does not inherently contain the **isolated** DNA segment of claim 7, and thus does not render this claim obvious.

Accordingly, in view of the foregoing, applicants respectfully submit that all claims comply with 35 U.S.C. §103(a).

In view of the foregoing, applicant respectfully submits that all claims are in condition for allowance. Early and favorable action is requested.

In the event that any additional fees are required, the PTO is authorized to charge our deposit account No. 50-0850.

Respectfully submitted,

Date: 5/7/01

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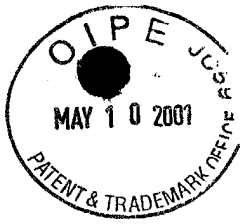

APPENDIX

The changes made by the amendments to the claims are shown below with insertions being underlined and deletions being bracketed.

5. An isolated DNA segment which hybridizes under stringent conditions to a DNA fragment having the nucleotide sequence set forth in SEQ ID NO.: 1 or a [unique] fragment thereof and codes for a MSH5 gene.

9. A vector containing an antisense DNA segment of the nucleotide sequence set forth in SEQ ID NO:1 or a [unique] fragment thereof.